

# How to Display Patterns inside Elementary Flux Modes.

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## BioSS Workshop

03/13/2017

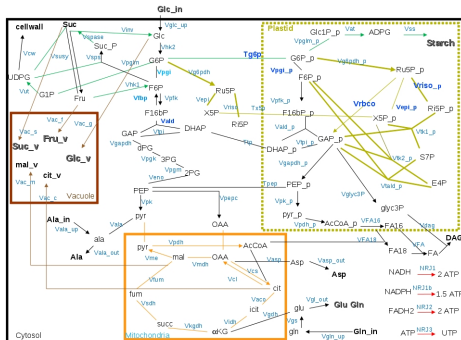
# Context

- Design of metabolic networks.
- Elementary Flux Modes analysis.
- Minimal Cut Sets to filter visual display of results.
- **Parallel coordinates** for visualization.

# Metabolic Network Design

## Building Metabolic Network

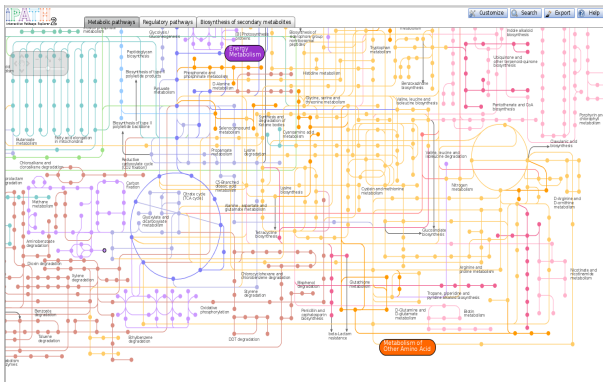
- More than hundreds of elements : enzymatic reactions and metabolites.
- Network description: nodes and edges.



# Metabolic Network Design

## Building Metabolic Networks

- Different models: reaction graph, metabolite graph or both.

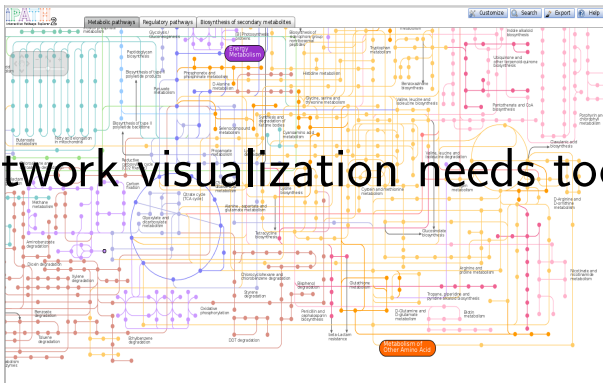


# Metabolic Network Design

## Building Metabolic Networks

- Network description: nodes and edges.
- Different models: reaction graph, metabolite graph or both.

Network visualization needs tools.



# Metabolic Network Design

## Flux analysis

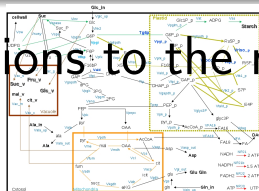
- Dynamic analysis :
  - Tools : Michaelis Menten equation, flux balance analysis ...
  - Requirements : quantitative information as kinetics of reactions
- Static analysis :
  - Tools : graph theory and linear algebra.
  - Requirements : qualitative and structural information as definition of the set of reactions, frontiers of the model ...

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Questions to the model.



# Elementary Flux Modes

## Definition

- EFMs are unique and minimal feasible pathways (S. Schuster, J. Bio. Sys. ,1995).
- Taking into account reversibility and stoichiometry of reactions.

## Computation

- Tools: CellNetAnalyser, EfmTools, RegEfmtools...



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## List of used reactions

(11) Tg6p (2 Vpgi\_p) (-2 Vpgi) (-3 Vfbp) (3 Vepi\_p) (-3 Vac\_g) (3 tr3) (-3 tr5) (3 node1) Gly\_p1 (3 t9PPPC) irreversible  
(12) Tg6y Vpgi\_p -Vpgi Vepi\_p Vinv -Vac\_g (-3 tr5) Vgdh node1 Vasp (3 t9PPPC) (2 VCO2) irreversible

## Matrix

```
1 0 2 -2 0 0 0 -3 0 3 0 0 0 -3 0 0 0 0 3 0 -3 0 3 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 3 0 ....
1 0 1 -1 0 0 0 0 0 1 0 0 1 -1 0 0 0 0 0 0 -3 1 1 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 3 2 ....
```

# Result Analysis

## Elementary Flux Modes

- Huge number of EFMs - several thousands.
- Classification:
  - Classical clustering: difficulties due to EFM properties.
  - Specific tools: dual computing of list of reactions leading feasible pathways.

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## Minimal Cut Sets

- **Idea:** find the reaction/set of reactions unable pathways.
- Taking into account reversibility of reactions and stoichiometry.

# Minimal Cut Sets

## Dual Problem: cutting flux

- Graph theory: searching the set of nodes building a minimal cut.
- Biology: consequences of stopping/missing the activity of an enzyme?

## Definition

- A MCS<sup>a</sup>, is a unique and smallest set of reactions whose removal from the network would stop a given metabolic function.
- Hope to obtain **less MCS than EFMs** for a given network.
- **93,009** MCS have been obtained by computation of the plant cell network vs **114,614** EFMs.
- Result too large to be analyzed like it.

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<sup>a</sup>Klamt et al J. Biol. 2004

# Central Metabolism of Plant Analysis

## Identification of network structure

- **Concrete example:** finding rules/constraints to produce 5 output metabolites if no entry of Glucose.
- Analysis of MCS with small size.

## Results

- MCS of size 2: Identification of a set of mandatory reactions.
- MCS of size 3, 4 ...: Identification of branches/switches through the network.

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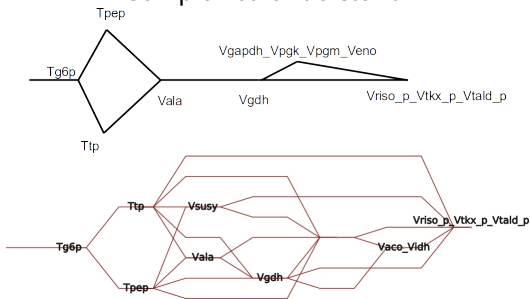
## Results

- MCS of size 2: Identification of a set of mandatory reactions.
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**How to visualize this information?**

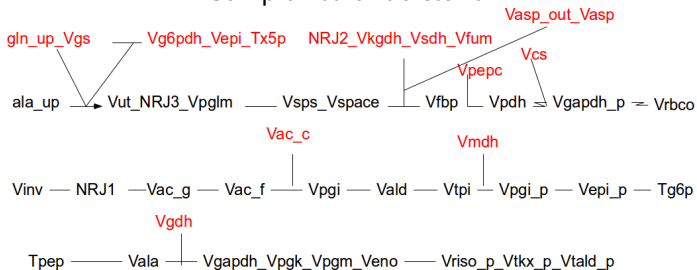
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Complex to understand!



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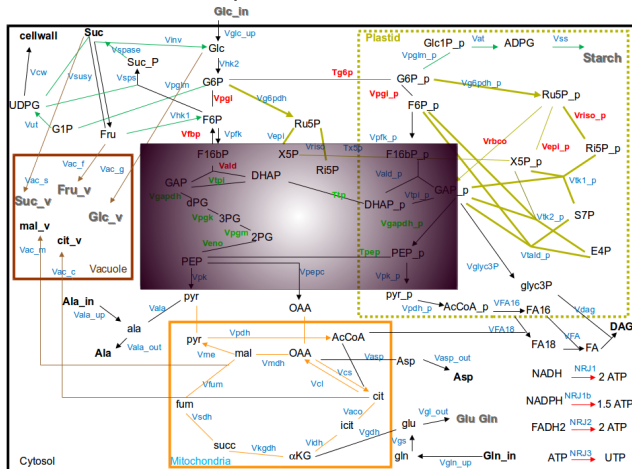
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# Graph display?

## Complex to understand!

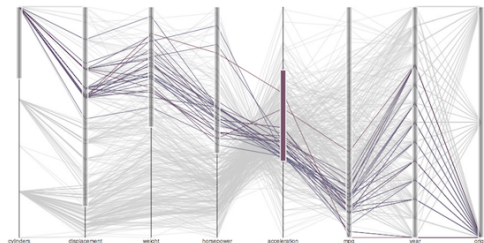


# Parallel Coordinates

## Methods

- Display a multivariate matrix: columns are data attributes, lines/polylines are elements<sup>a</sup>.
- Attributes are vertical axes.
- For big data set, polylines can be aggregated in groups.

<sup>a</sup>Inselberg, Visual Computer, 1985



from <http://mbostock.github.io/protovis/ex/cars.html>

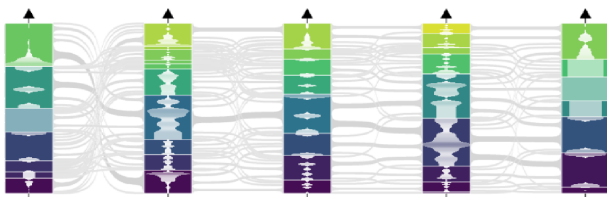
# Parallel Coordinates

## Visualization of EFM

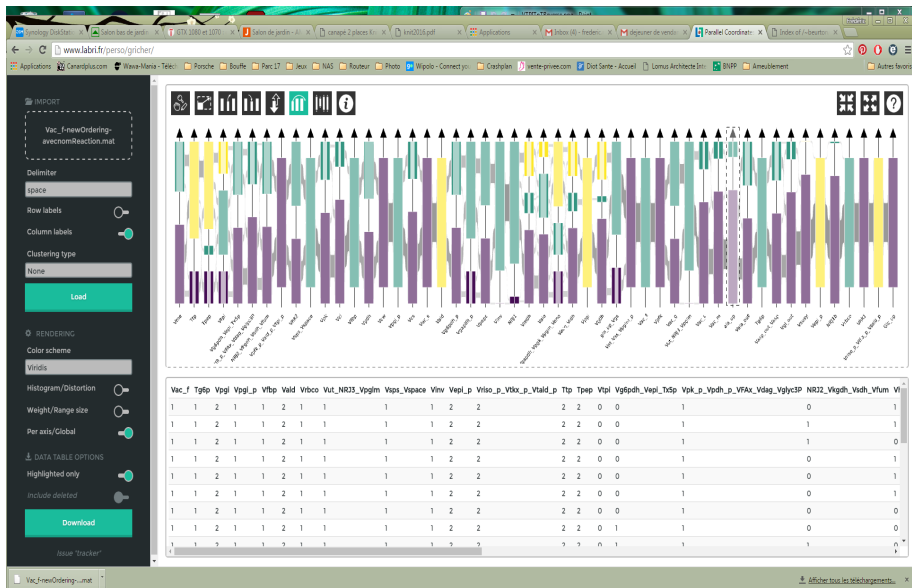
- Vertical axes are reactions, lines are EFM.
- Values on axes present information about **absence** (0) of a reaction or about its **forward** (1) or **backward** activity (2).

## CoPHI: Parallel Coordinates Highly Interactive

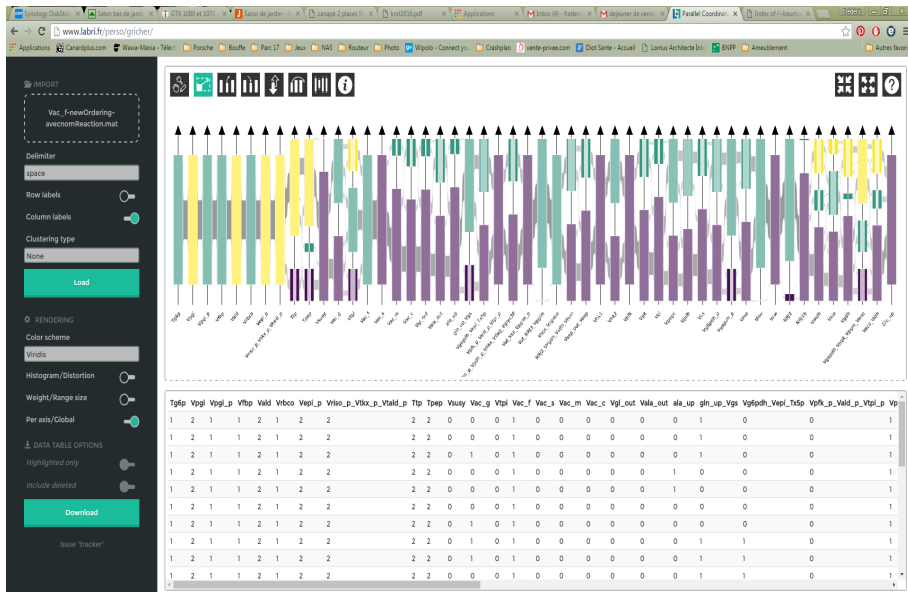
- Web application - javascript environment.
- Developed by Joris Sansen and the MaBioVis team at LaBRI (<http://www.labri.fr/perso/jsansen/>).



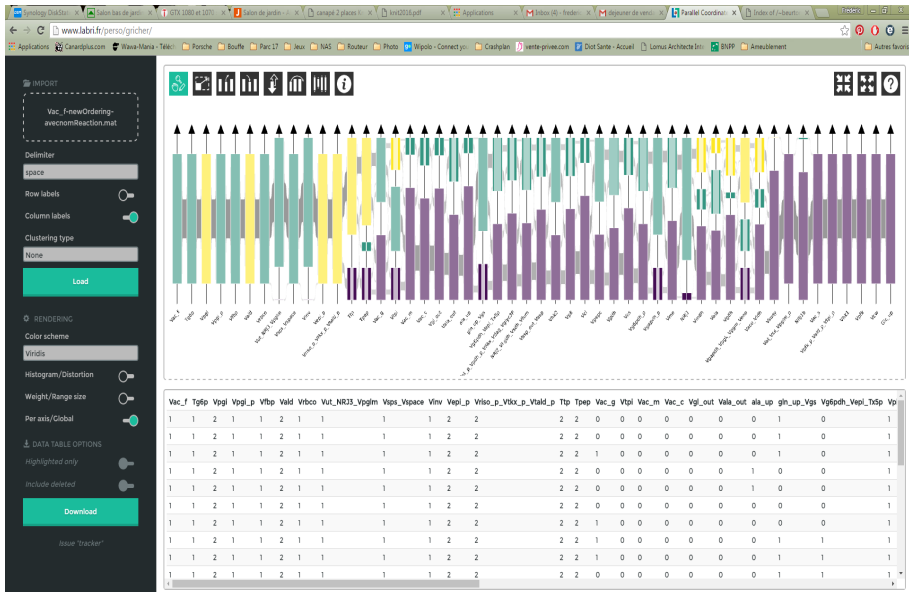
# COPHI



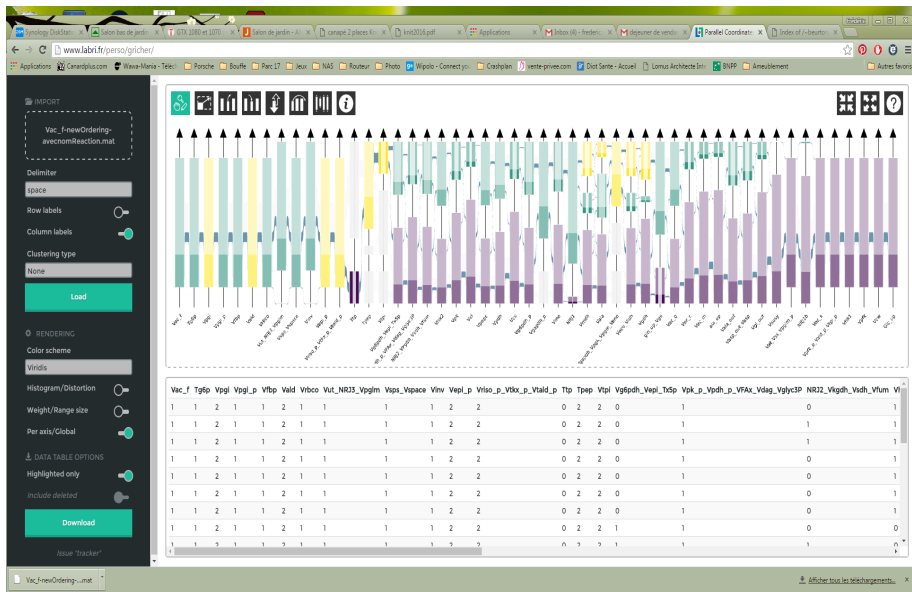
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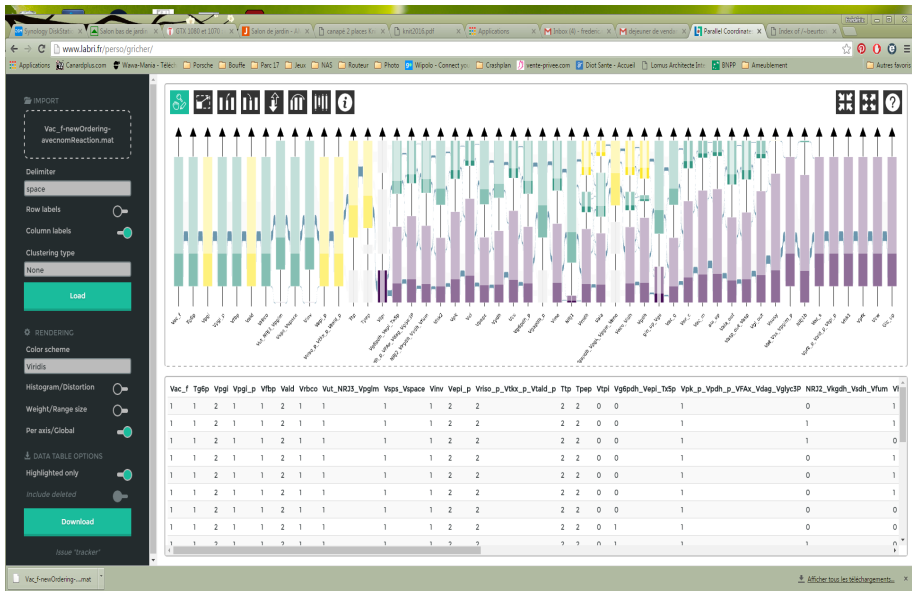
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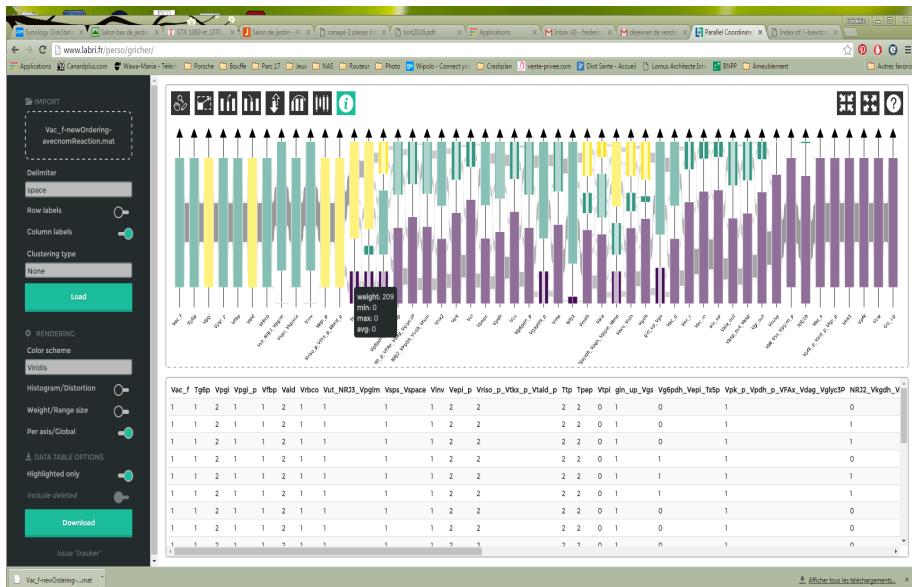


CoPHI





# CoPHI



# Conclusion

## Leave graph design

- Another way to display connections through the network.
- Global view of selection.
- Rate of EFM's concerns by response to the question.

## Dynamic interface driven by pre-treatments

- Pre-treatments lead by the biological questions.
- Dynamic interface to explore possibilities.
- Changing the way to consider displaying of metabolic graphs.